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THE PRESENT STATUS AND PROBLEMS OF BACTERIAL CHEMOTHERAPY[1]

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SUCCESSFUL chemotherapy of bacterial diseases is an innovation of the last four years only; in the history of medical progress it is a newborn babe—a lusty infant with powerful lungs and an incredible capacity for growth. Have its shoutings and precocity been justified and have its growth and development been directed along the right paths?

Chemotherapy, in the case of protozoan infections, can be considered to be of comparatively ancient origin. The sixteenth-century use of mercury in syphilis and the seventeenth-century use of cinchona bark in remittent fevers and of ipecac in dysentery are examples of a specific form of therapy which was later designated "chemotherapy." All three of these drugs are old and popular remedies and were used without a knowledge of the etiology of the disease or of the mode of action of the remedial agent. Although Koch in 1881 reported unsuccessful attempts at bacterial chemotherapy in anthrax infections of guinea pigs, real experimental chemotherapy began with the very significant experiments of Ehrlich and Shiga in 1904. Their report of the cure of an otherwise fatal trypanosome infection in mice by one injection of the dye trypan red marks the beginning of a new epoch, despite the fact that animals other than the mouse were not cured and that the drug was of no practical use. This work led in 1910 to the well-known discovery of the therapeutic effect of organic arsenic com-

[1] This paper was given before the Society of the American Bacteriologists, New Haven, December 28, 1939.

pounds in spirochaetal diseases. Arsphenamine and neo-arsphenamine were the first synthetic organic compounds to be used successfully in chemotherapy.

Thirty years have elapsed since Ehrlich's momentous discovery and we can inquire what advances have been made. Although we now have drugs of quite different chemical constitution—dyes of the trypan red group, acriflavine, styryl-quinoline compounds, organic arsenic compounds, compounds of antimony and bismuth, and certain colorless non-metallic compounds favorably influencing experimental trypanosome infections, the synthetics plasmoquin and atebrin as substitutes for quinine in malaria, and such drugs as carbarsone and chiniofon for amebic dysentery—I think it is fair to say that progress in the field of protozoan chemotherapy has been quite slow. The organic arsenicals are still the sheet-anchor for the treatment of syphilis. These drugs are given by injection and no leads toward finding non-metallic compounds effective in syphilis appear to have been discovered. Moreover, there is as yet no completely satisfactory and generally accepted explanation of the mode of action of any chemotherapeutic drug in any protozoan disease.

The bacterial diseases were considered until recently to be resistant to chemotherapy; the bacteria were thought too primitive in structure to be influenced by chemicals which were not highly toxic to the host. Many attempts had been made to cure bacterial infections in animals by the use of drugs, but these all met with little or no success with the exception of Morgenroth and Levy's finding in 1911 that ethylhydrocuprein would cure mice of a pneumococcus infection. The effective dose of this compound, however, was very near the lethal one, and the experiments were of no real clinical service.

This situation has been radically altered by the discovery of the sulfonamide derivatives as bacterial chemotherapeutic agents. The known scope of effective treatment with these compounds is widening rapidly, and brilliant success has already been achieved, but so much ground remains to be explored that the ultimate consequences of the discovery are beyond prediction. The history of this recent development of bacterial chemotherapy is too well known to need repetition—the landmarks are Gelmo's synthesis of sulfanilamide in 1908, Mietzsch and Klarer's patent of the azo dye "prontosil" in 1932, Domagk's report on the curative effects of "prontosil" in streptococcus infection in mice in 1935, and the announcement by the Tréfouels, Nitti and Bovet, later in that year of the activity of the simple organic compound, sulfanilamide.

Although sulfanilamide (and allied drugs) were first thought to have a specific action on the streptococcus alone and to be incapable of influencing other infections, it has now been definitely proved that these drugs are effective in a wide variety of experimental infections in animals and a number of infectious diseases in man. Thus the therapeutic effect of sulfanilamide (or allied compounds) is excellent in experimental mouse infections due to the β-hemolytic streptococcus, meningococcus and pneumococcus. It is still good, but less satisfactory in mouse infections produced by strains of gonococcus and staphylococcus; Proteus, colon, typhoid and paratyphoid organisms; the Sonne strain of the dysentery bacillus; a strain of Listerella; Hemophilus influenzae, the Welch bacillus, and certain members of the Pasteurella group, including the plague bacillus. Prolongation of life, with few or no survivals, is reported for infections produced by strains of Salmonella typhimurium, Friedländer's bacillus; Pasteurella pseudotuberculosis and the anthrax bacillus. A definite inhibitory effect on the development of experimental tuberculosis in the guinea pig and rabbit, an alteration of the natural course of experimental Brucella infections in guinea pigs and Bacterium necrophorum infection in rabbits, and the remarkable curative effect in certain human urinary tract infections also attest to the wide-spread antibacterial powers of the sulfonamide group of drugs. In protozoan infections, the only conclusive evidence of effectiveness is that reported for malarial infection of monkeys. In virus infections the results so far obtained are negative or inconclusive, with the exception of lymphogranuloma venereum and trachoma. In both of these cases, there is some doubt if the infecting agent can be classed as a true virus.

The above attempt to classify roughly the efficiency of sulfonamide compounds in various infections may be subject to considerable revision when more accurate experiments are available. We know now that very marked differences in susceptibility between different strains of the same organism occur and usually only one strain of the particular organism has been used in the investigations upon which the above classification is based. Also, the low virulence for mice of certain organisms and the necessity of using mucin to enhance this virulence in certain experiments may cause errors in comparisons with other experiments where organisms of very high virulence serve as the infecting agent. The use of different methods of dosage of the drugs is another important factor that may disturb such comparisons as the above (this will be referred to more fully later). Lastly, the possibility of the favorable results being due to the cure of some secondary infection and not the primary one must be considered; the favorable therapeutic results of these drugs reported in elephantiasis of filarial origin and in smallpox are probably due to an action on the secondary streptococcal infections.

These almost pan-antibacterial properties of sulfanilamide and allied compounds represent, indeed, an enormous advance in the field of bacterial chemotherapy, but no end of problems still need investigation. It appears that in general α-hemolytic streptococci and anerobic streptococci are much more resistant to these drugs than the β-hemolytic class; within the class of β-hemolytic streptococci, group D appears very resistant and evidence exists that certain strains of other groups are very resistant to the action of these drugs. The therapeutic efficiency of this group of drugs has been tested against various types of pneumococci, but it now appears that as much or more difference may exist between strains of the same type as between types. Similar relations probably obtain in other genera of bacteria which are susceptible to these drugs.

Another question of prime importance is that of the specificity of these drugs in bacterial infections. In the case of the chemotherapy of protozoan diseases, we know that quinine and atebrin are active in malaria, the organical arsenicals and bismuth in syphilis, germanin and tryparsamide in trypanosomiasis and emetin and carbarsone in amebic dysentery, but that interchange of drugs and diseases can not be made. Are the sulfonamide drugs active in some degree on all bacteria and do the more potent drugs simply act on a larger range of infections than the less potent ones? Do these drugs have some degree of activity in all infections where death results from rapid multiplication of bacteria, and fail only in infections where a small number of bacteria can form a toxin sufficiently potent to kill the animal, as in tetanus and diphtheria? Or is there a real specificity of the drugs for different bacteria, as in protozoan chemotherapy? Accurate data are needed to answer these questions before the best use of these new chemical weapons or the quickest evolution of new ones can be attained.

One difficulty in answering definitely the above questions is that the data available in the reports of various investigations give more of a qualitative than a real quantitative comparison of different drugs or of the same drug under different conditions. Some of the reasons for this appear to be as follows. Relatively simple methods suffice for detecting anti-bacterial activity of drugs *in vivo*, but a more elaborate procedure is required to evaluate such activity quantitatively. Data on the effectiveness of drugs have been obtained in most cases by administration of doses according to schedules which have differed with each investigator. Extreme variations of drug concentrations in the blood must have resulted from the various dosage schedules employed, as well as from differences in absorption, excretion and distribution of different drugs. With many drugs administration at intervals greater than six hours has resulted in high concentrations of short duration followed by periods when little or no drug was present in the blood. The lack of a suitable therapeutic response as an end-point and of a standard for comparison, as well as complete ignorance of the accuracy of the comparison, has invalidated quantitative conclusions from many experiments.

A paper has just appeared from our laboratory on the experimental basis for a method for the quantitative evaluation of the effectiveness of chemotherapeutic agents against streptococcus infection in mice. A considerable amount of as yet unpublished data obtained with this method would indicate that it gives a more or less absolute comparison of the effectiveness of different drugs or of the same drug under different conditions in both streptococcus and pneumococcus infections in mice. The method in brief is as follows. A more or less constant blood concentration of drug during the period of therapy is maintained by using food in which the drug has been incorporated. By treating mice in individual cages the daily drug intake of each mouse can be determined. Drug diets are so selected that one may expect to obtain with different drug intakes survival percentages greater and less than fifty. The diets are fed for one or more days prior to and for the desired period after infection. Irrespective of the percentage of drug in any diet, the average daily drug intakes (per mouse) can be arranged in groups and correlated with percentage survivals. The dosage-survival curve is now computed and the *Median Survival Dose* ($S.D._{50}$) with its standard error obtained. This can be converted into the *Median Survival Blood Concentration* ($S.B.C._{50}$) by a factor which relates blood concentration to daily drug intake of the drug being tested. By using a standard, one obtains a comparative value for the S. B. $C._{50}$'s which may be nearly absolute, even though the S. B. $C._{50}$'s themselves are variable. It is hoped that the use of this method or some improvement along the same lines will yield data of sufficient accuracy to give unequivocal evidence for or against ideas which are now mostly a matter of opinion or guesswork.

Nearly all research directed toward bacterial chemotherapy of experimental infections has utilized the mouse as the experimental animal. The reasons for this choice are not difficult to surmise: the susceptibility of the mouse to certain strains of streptococci, pneumococci and many other bacteria of human origin, the availability of more or less pure strains, the ease with which large numbers of these animals can be handled and their relatively low cost are probably mainly responsible for the use of these rodents. Very few investigations have been concerned with the therapeutic effect of the sulfonamide type of compounds in experimental infections in animals other than the mouse. In practically all cases where one of these

drugs has been introduced into clinical use as a bacterial chemotherapeutic agent, experimental therapeutic studies in the mouse have been transferred directly to man. Fortunately, the transfer from the lowly mouse to man has been justified in most instances, but the history of protozoan chemotherapy should lead us to fear that this will not always be so. The rapidly fatal infection in the mouse is obviously not similar to infection with the same organism in human beings, and, I think, there is a great need of developing satisfactory methods for studying experimental infections in other animals which may resemble the human more nearly as regards size and phylogenetic relationship. Another reason for the use of animals other than the mouse lies in the fact that such comparative therapeutic research may give valuable information as to the importance of the host factor in the mechanism of action of these drugs. Infection of animals of different species with the identical organism and quantitative study of the effects of therapy with the same drug should yield information of value. The reason that these drugs are ineffective against a strain of streptococcus of low mouse virulence has been stated to be due to the large number of organisms necessary for a fatal infection. In support of this is the observation that when mucin is used to reduce the lethal dose, effective therapy with sulfanilamide is obtained. When it is remembered, however, that fatal infections produced by the injection of large numbers of staphylococci and other bacteria can be successfully treated, it would appear that more investigation is needed. It is possible that the reason for the difference between infections of low and high virulence may be found in experiments on different species of animals.

This discussion of experimental therapy can not be closed without a word about the important matter of dosage. It has frequently been stated that it takes ten to twenty times as much sulfanilamide (or allied drug) to cure an experimental streptococcus infection in the mouse as to cure an infection with the same organism in man. Such statements still occur in the current literature. This idea is based on the amount of drug given per kilogram of body weight. As an actual fact, experimental infections in the mouse respond to blood concentrations of these drugs which are certainly not higher but probably lower than those effective in infections with the same organism in man. The erroneous conceptions of dosage are due to several facts, namely, that different schedules are used by mouth, that dosage between mouse and man is not directly related to body weight, and that the mouse absorbs and excretes many of these drugs much more rapidly than man. It takes more than ten times the daily dose, on the basis of body weight, to give the same blood concentration in the mouse as in man. I do not believe that any real scientific justification exists for the *size* of the doses employed at present in patients; what has been developed is empirical but probably the best that can be done at present. Until more is known in a quantitative way about strain susceptibility and resistance of various organisms to these drugs, one is not justified in experimenting with human dosage in serious infections. It is important to realize that this group of drugs is the only one in all therapeutics where the dose is based upon blood concentration, where sound experimental observations justify the *schedule* of dosage, and where a maintenance of a constant blood concentration over several days is attempted. This is probably owing to the fact that these drugs are given in such quantities that it has been fairly easy to devise accurate and simple methods for determining their concentrations in the blood.

We come now to a consideration of an equally important side of the subject of bacterial chemotherapy, namely, the effects of the drug on the host. This involves a determination of toxicity, of the action of the drug on individual organs and tissues, of the absorption, excretion and distribution of the drug and of the fate of the drug or changes undergone by it in passing through the host. These points are all considered in orthodox pharmacology in the investigation of any new drug, but I think that certain departures from the orthodox methods are necessary in studying these newer antibacterial drugs.

In connection with toxicity, it seems obvious that both acute and chronic toxicity should be determined on several species of animals. In addition, for the subacute or chronic toxicity, we should know the blood concentration which, when maintained for several days, produces toxic symptoms—the same method being used to determine the toxicity as when the drug is administered for its therapeutic effect. There is good evidence to believe that a blood concentration which is innocuous if maintained for only a few hours may prove quite toxic if maintained hour after hour for several days. One must also remember that toxicity is not altogether a matter of life and death; the limiting factor in the use of these drugs is generally some toxic manifestation which does not kill the patient. We need more determinations of this kind of toxicity in animals, the relative effect of these drugs on the blood, cerebral cortex, vomiting center, kidneys, liver, etc., and also the development of methods for assessing on animals the ability of the drugs to produce reactions which in men are due to hypersensitiveness and idiosyncrasy.

In determining toxicity by giving drugs by mouth, there is a pitfall into which many have fallen—the reporting of a substance to be of low toxicity, when this is due to its poor absorption from the gastrointestinal tract. In my opinion, we are no more justified in considering such a substance as non-toxic than we

would be in the following instance. Barium sulfate given by mouth is not absorbed into the body; it remains *outside* of the body and hence is not toxic. To conclude from this experiment that barium is nontoxic is about the same as concluding that potassium cyanide is not toxic because I can carry a well-stoppered bottle of several hundred grams in the pocket of my coat without experiencing any ill-effects. We need to know the effects of these drugs after they have gained access to the blood and tissues; we should base toxicity on the relative blood concentrations which produce equal responses.

While the effects on the host of sulfanilamide and sulfapyridine have been investigated in some detail, the effects of other drugs of this group which are used clinically are not known in any detail. Such a state of affairs is unfortunate and needs correction if real scientific advance is to continue. To cite one point only, the rapid diffusion and penetration of sulfanilamide to all parts of the body is undoubtedly one of the factors which makes the substance a successful chemotherapeutic agent. This does not occur with the same readiness with all drugs of this group: accurate data on those to be used in the patient are important.

The intelligent use of any drug demands that its mechanism of action shall, if possible, be understood, and the logical method of attacking the problem of substitutes for use in place of sulfanilamide or in infections in which this drug fails would appear to be the discovery of how sulfanilamide acts. It is not surprising that in the very short time that intensive work on sulfonamide derivatives has been pursued no satisfactory explanation of the mechanism of action has been found, for in the chemotherapy of no protozoan diseases is there as yet any complete and generally accepted explanation of the mode of action of the drug. The subject of the mechanism of action is obviously very important and justifies intensive work: There is reason to believe that the attack upon this problem may be more fruitful of results in the case of bacterial than in that of protozoan chemotherapy.

Time will not permit, nor do I think it worth while to attempt to trace in detail the numerous studies on the mechanism of action of these drugs; the subject has been frequently reviewed and will be the topic of our round table discussion to-night. All observers seem to agree that sulfanilamide inhibits the growth of the invading organisms and that this alone may be sufficient to control the infection but not to eradicate it without the cooperation of the defense mechanism of the host. Many chemical compounds are bacteriostatic or bactericidal in high dilution *in vitro,* but have no action on infections *in vivo* at all comparable to that of the sulfanilamide group of drugs. More than high bactericidal properties *in vitro* is necessary to make a drug an effective chemotherapeutic agent: Low toxicity to the defense mechanisms of the host and penetration of all tissues and organs may be quite as important as bactericidal properties. I should like to point out the need for accurate and quantitative data upon which to base and by which to test out theories of mode of action. Such data should cover the many ramifications of this field; such as *in vitro* studies, the nature of the curative process in infected animals, the relation of *in vivo* activity of various compounds, correlation of the metabolism and biochemical behavior of various organisms with their resistance or susceptibility to these drugs, the curative effect of the drugs on the same organism in different hosts, the question of changes of the drug by the host or infecting organism, and the effect of changes in chemical constitution on the activity of a drug. It is only when a broad outlook on the whole problem is taken that the true mechanism of action will be revealed. Methods are lacking at present for a quantitative study of many of these problems.

The situation referred to above is well illustrated by the present status of *in vitro* studies. The data so far published are discordant and contradictory; different workers have reported that concentrations of sulfanilamide of 10 to 20 mgm. per cent. may result in experiments on streptococci in no effect, in bacteriostasis and in bactericidal effects. Obviously, fundamental studies of the variables encountered in *in vitro* experiments must be undertaken. As a result of such studies we know now that the strain of streptococcus, the size of the initial inoculum, the composition of the medium, and the temperature at which the test is performed may have a marked effect on the result obtained. More carefully controlled and quantitative work *in vitro* is needed under different conditions before the true *in vitro* activity of these drugs can be defined.

Another very important problem is the relation of chemical constitution to antibacterial action. This is simply a part of the broader problem of the relation of chemical constitution to pharmacological action, one of the important problems of pharmacology, but one about which comparatively little is known. Although over a thousand chemical compounds of the sulfonamide type have been prepared and tested for their therapeutic effect in infected mice, only qualitative conclusions can in general be drawn because few comparisons of active substances have been made in a really quantitative manner. Neither the sulfonamide group nor sulfur in the molecule is necessary for activity. With few exceptions, all the compounds which are active contain a nitro, amino or substituted amino group in the para position on the benzene ring. The exceptions need to be examined more carefully.

Active compounds related to sulfanilamide can be divided into two classes: the first where there is substitution in the amino group, and the second where there is substitution in the sulfonamide group. To the first class belong such compounds as prontosil, neoprontosil, and N^4-benzylsulfanilamide; to the second, such substances as sulfapyridine, sulfathiazole and N^1-acetylsulfanilamide (Albucid). It is probable that substances of the first class owe their activity to their decomposition to sulfanilamide. Although it has been shown definitely that sulfanilamide is formed from these substances in the animal body, it has not been proved that their activity is entirely explained by this. Quantitative comparison of the effectiveness of the same blood concentration and duration of sulfanilamide as obtained from these substances with that obtained by giving sulfanilamide itself is necessary to solve the problem. The sulfanilamide derivatives of the second class are apparently not decomposed in the body and owe their activity to the compound as such. Although not proved, it is probable that nitro compounds act through the amines known to be formed from them.

Numerous other problems might be discussed if time permitted. To mention only a few. Can we obtain a substitute for sulfanilamide with the same activity but less toxicity to the host, or are activity and toxicity intimately linked together? Sulfapyridine, although highly effective, would not seem to be the final answer to the pneumococcus problem. More active drugs against viridans, staphylococcus, tuberculous and other infections are needed, and the whole question of the action of this group of drugs on virus infections needs careful investigation. The relative value of drug and serum and drug alone may be of importance in different types of infection. The marked susceptibility of fungi *in vitro* suggests the trial of these drugs in mycotic infections, while their definite bactericidal action *in vitro* reopens the question of local use.

In conclusion, there is no doubt that bacterial chemotherapy already occupies an important role in the therapy of infectious diseases, and with the solution of more and more of its problems will probably increase in importance. This lusty young infant in therapeutics can hold its own against its father—protozoan chemotherapy—and can even possibly aid it. Ehrlich's aim in chemotherapy was to make a success of the method of *Therapia magna sterilisans*, to destroy the invading parasites within one or two days by a single dose of a drug. Although a certain amount of success with this method was achieved in certain experimental infections in animals, it has not been successful in human diseases of protozoan origin. The alternative was adopted of administering repeated doses separated at intervals. These intervals were frequently sufficiently long to allow the previous dose to disappear from the body. In bacterial chemotherapy, it is now known that maintenance of a more or less constant concentration of drug in the blood and tissues day and night is necessary for the most effective therapy: Both an effective blood concentration and a sufficient duration of this concentration are necessary. To accomplish such a course of therapy, dosage must be thought of in terms of blood concentration and duration rather than in terms of the amount of drug administered. This method should be considered in protozoan chemotherapy; the results already reported in the arsenotherapy of syphilis by the continuous intravenous drip method are encouraging. The method of dosage introduced by bacterial chemotherapy may after all be considered a return to Ehrlich's *Therapia magna sterilisans* with a maintained blood concentration of drug replacing the single massive dose.

SCIENTIFIC EVENTS

THE ENGINEERING SOCIETIES LIBRARY[1]

THE Engineering Societies Library has made available at cost not only photostats, but also microfilm copies of material contained in the 160,000 volumes and thousands of periodicals in its collection. Regardless of residence, any engineer, library or company may order an 11 × 14-inch white-on-black (negative) photostat print on bromide paper at 30 cents each, which charge includes ordinary postage to any part of the world. Black-on-white (positive) prints are supplied by copying a negative print, which makes the cost 30 cents additional. Microfilm copies on 35-mm film are available at a cost of four cents per exposure (usually one page), with a minimum charge of $1.25 per volume.

Each photostat print contains one or two pages of the original article depending on its size. Reductions to approximately one half or enlargements to twice the original size can be made, if desired, without any extra charge. Unless an enlargement or reduction is specified, prints are made the same size as the original.

For the benefit of those who can come to the library in person, a trained staff stands ready to assist them in their problems. Despite the fact that it is the official library of national engineering societies, all

[1] The library is a joint cooperative enterprise of the American Society of Civil Engineers, the American Institute of Mining and Metallurgical Engineers, the American Society of Mechanical Engineers and the American Institute of Electrical Engineers.

books and periodicals of the library are available for the free use of the public during regular hours. If a translation or list of references on any particular subject is desired, the library staff will prepare this at cost. For those wishing to photograph material in the library, a photographic copying stand, complete with table and electric lights, is available for use with the visitor's own camera.

THE SUMMER MEETINGS OF THE AMERICAN SOCIETY OF PLANT PHYSIOLOGISTS

THE national meetings of the American Society of Plant Physiologists will be held in Seattle, Washington, from June 18 to 22. The program includes three symposia:

1. A symposium on photosynthesis jointly with the Botanical Society of America. This symposium stresses work done in the West and will have a broad educational character.
2. A symposium on aquatic botany also to be held jointly with the Botanical Society of America.
3. A symposium on phosphate nutrition to be held jointly with the Society of Soil Scientists.

A joint meeting with the Society of Horticultural Science is planned.

Three half days have been reserved for submitted papers. Those wanting to present papers are strongly urged to send in titles as soon as possible, and to reach the secretary of the Western Section at the California Institute of Technology, Pasadena, California, not later than April 27.

An excursion to the Oceanographic Laboratories of the University of Washington at Friday Harbor is planned on June 22. This provides an opportunity to become acquainted with the beautiful Puget Sound area. Those planning to participate are requested to get in touch with the secretary of the Western Section so that arrangements can be facilitated.

J. VAN OVERBEEK,
Secretary, Western Section

WESTINGHOUSE RESEARCH FELLOWSHIPS

ANNOUNCEMENT of appointments of the third annual group of five Westinghouse Research Fellows has been made by the Westinghouse Research Laboratories. The appointees were selected from a group of forty-two applicants for fundamental research in physics, chemistry, mechanics and metallurgy. The men selected are:

DR. JERALD E. HILL, *University of Rochester*, for research in nuclear physics with the large electrostatic generator. Dr. Hill will be particularly interested in measuring thresholds and excitation functions for proton-neutron reactions.

DR. SIDNEY KRASIK, *Cornell University*, for research on fundamentals of velocity-modulated electron beams as generators of ultra high frequency radiations. Dr. Krasik has been associated with Professor L. P. Smith, of Cornell, in electronics research.

DR. WALTER KAUZMANN, *Princeton University*, for research in application of the absolute reaction-rate theory of chemical kinetics to liquid flow and solid plasticity problems. Dr. Kauzmann is also interested in the study of the solvent effect on optical rotatory power as a tool for studying molecular interactions in liquids.

DR. FREDERICK W. STALLMAN, *University of Illinois*, for research in nuclear physics. Dr. Stallman is particularly interested in the study of the photo-disintegration of the deuteron by gamma rays and of the angular distribution of the protons produced in this way.

DR. DAVID P. STEVENSON, *California Institute of Technology*, for research in chemical bond resonance energies with the aid of the mass spectrometer. Dr. Stevenson is also interested in the study of resonance energies by use of gaseous electron diffraction methods.

The aims of the company in establishing the fellowships are:

1. To make a worth-while contribution to the development of the fundamental sciences on which modern industry is based. The company feels that all research leading to a better understanding of matter and energy will ultimately prove valuable to technology even though the immediate field of application is not apparent.
2. To enable a group of able investigators to become familiar with the scientific problems confronting the electrical industry. It is believed that this contact will be of great value whether the men turn to industrial research or to academic work after completion of their fellowship period.

Fellows will devote their entire time and energies to work on their research projects at the Westinghouse Research Laboratories. The usual two weeks' vacation at the end of each year, together with liberal time for attendance at scientific meetings and for visits to other laboratories will be allowed.

It is expected that fellows will also participate in the seminars and colloquia held at the laboratories and in the neighboring institutions of higher education. From time to time progress reports will be expected and a final report in form suitable for publication will be required toward the end of the fellowship period.

Appointments are made for a period of one year and fellows are eligible for one reappointment for a like period. The salary will be paid semi-monthly at the rate of $2,400 a year.

The laboratories include the following six divisions —mechanics, electromechanics, electrophysics, chemical and metallurgical, magnetic and insulation. The work of the fellows will be carried on within the appropriate division under the general supervision of Dr. E. U. Condon, associate director.

ELECTION OF FELLOWS OF THE ROYAL SOCIETY

AT the meeting of the Royal Society on March 14, the following were admitted to fellowship;

ASTBURY, W. T., reader in textile physics in the University of Leeds, distinguished for his pioneer researches into the structure of natural fibers and proteins. His chemico-x-ray technique has opened up new fields of knowledge.

BEER, G. R. DE, reader in embryology, University College, London, distinguished for his original contributions on the embryology of vertebrates which are notable for their completeness and accuracy.

BULMAN, O. M. B., university lecturer in paleozoology, Cambridge, distinguished for his work on Lower Paleozoic stratigraphy, especially on the morphology, ontogeny and phylogeny of the Graptolites and their geological history.

CADMAN OF SILVERDALE, BARON, chairman of Anglo-Iranian Oil Company; emeritus professor of mining and petroleum technology, University of Birmingham, distinguished for his many public services and for his leadership, administrative and scientific, in the development of the Iranian oil-fields.

COOK, G., Regius professor of civil engineering and mechanics, University of Glasgow, distinguished for researches into a wide variety of engineering problems and particularly for original investigations into the stress-strain relations of metals when passing from the elastic to the plastic state under systems of combined stresses.

DAVENPORT, H., lecturer in mathematics, University of Manchester, distinguished for his work in pure mathematics and particularly for his contributions to the theory of numbers.

GOODEVE, C. F., reader in physical chemistry, University College, London, distinguished for his work in many branches of physical chemistry and particularly for his contributions to our knowledge of absorption spectra and photochemistry.

GREGORY, F. G., professor of plant physiology, Imperial College, London, distinguished for his researches on the analysis of plant growth, especially in relation to mineral nutrition and vernalization.

HARDY, A. C., professor of zoology and oceanography, University College, Hull, distinguished for his researches on marine biology and their application to fishery problems, with special reference to the ecology of the herring and the distribution of plankton.

KELLAWAY, C. H., director of the Hall Institute for Medical Research, Melbourne, Australia, distinguished for his researches on snake venoms and on protective antisera.

KRISHMAN, K. S., Mahendralal Sircar research professor of physics in Calcutta, distinguished for his researches in optics and especially for the study of the influence of magnetism on crystals.

LINSTEAD, R. P., professor of organic chemistry, Harvard University, distinguished for work in synthetic organic chemistry, including reversible isomeric change.

MAASS, O., Macdonald professor of physical chemistry, McGill University, distinguished for his researches in physical chemistry, particularly those relating to the properties of gases and liquids, during which he has detected and studied an important and anomalous behavior in the critical region.

MASSEY, H. S. W., Goldsmid professor of mathematics, University College, London, distinguished for his work in mathematical physics and particularly for his contributions to the quantum theory and its applications to physics.

MATTHEWS, B. H. C., assistant director of research, Physiological Laboratory, and fellow of King's College, Cambridge, distinguished for his work on electrophysiology, particularly in connection with the sense organs and the spinal cord, by which important factors in the mechanism of the nervous system have been revealed.

PEARSALL, W. H., professor of botany, University of Sheffield, distinguished for his investigations on the determination of the factors underlying the distribution of aquatic plant communities, especially in the British lakes, and on the conditions affecting algal metabolism.

QUASTEL, J. H., biochemist to the Cardiff City Mental Hospital, distinguished for his work on chemical reactions in resting bacteria, the mode of action of enzymes, the chemical metabolism of the brain and the action of drugs.

ROBERTSON, A., professor of mechanical engineering, University of Bristol, distinguished for his fundamental contributions to knowledge relating to the stability and strength of solid and tubular struts, and to many other problems in the field of the strength of materials of engineering construction.

SPATH, L. F., lecturer in geology at Birkbeck College, University of London, distinguished for his researches on the phylogeny of the Nautiloidea, the geniatites and the ammonites, and particularly on the problems of ontogeny and recapitulation in cephalopods.

SUCKSMITH, W., reader in magnetism, University of Bristol, distinguished for his outstanding experimental researches, particularly on the gyromagnetic effect of paramagnetics and the physical properties of ferromagnetics.

THE EIGHTH AMERICAN SCIENTIFIC CONGRESS

ATTENTION was called in the issue of SCIENCE for November 24 to the eighth American Scientific Congress that will be formally opened in Washington on the evening of Friday, May 10. The ceremony will take place at the Pan American Union. There will be present members of the President's Cabinet, members of the Congress of the United States and the various diplomatic representatives of the other American republics, as well as the delegates and participants in the congress.

Registration and the preliminary organization of the sections will occupy the entire first day of the congress. The registration office, which will be at the Pan American Union headquarters, opens on Monday, May 6.

The organization of all sections will be completed on the morning of Saturday, May 11. That afternoon the delegates will visit Mount Vernon.

On Saturday evening all the delegates and participants in the congress are invited to the official reception, which will take place at the Pan American Union. There will be present again members of the President's Cabinet, members of the Congress of the United States and representatives of the Diplomatic Corps.

A motor trip through the springtime countryside of Virginia will feature the program for Sunday. The route will pass through some of the historic battlefields of the American Civil War and through a portion of the colonial section of Virginia, having as its terminus the Caverns of Luray. The delegates will lunch at Luray before returning to Washington in the afternoon. A portion of the Skyline Drive which tops the crest of the Blue Ridge Mountains, attaining a height of almost four thousand feet, will also be visited *en route*.

The first plenary session of the congress will take place on Monday, May 13. The official luncheon, at which the governmental delegates of the other American republics will be the guests of the United States Government, will take place immediately after the first plenary session. The afternoon of this same day will be devoted to the business of the various sections. There will be no congress activity on Monday evening, in order that the various sections may arrange for special business or social meetings.

Tuesday will be devoted entirely to meetings of the various sections. The chairmen of some of the sections plan special visits of technical interest during that day or those that follow. There will be certain other features of general interest in which the whole congress will participate. That evening all delegates and participants are invited to a special symphony concert which will be given in their honor.

Wednesday morning and early afternoon will be devoted to congress matters. That afternoon the delegates will be guests at a garden party in their honor.

On Thursday, after a full day of sectional meetings there will be held the official banquet of the congress, at which the official delegates will be the guests of the United States Government.

The final meetings of the various sections will be held on Friday morning, and the final plenary session of the congress will take place the same afternoon.

Later that afternoon, the delegates will go by steamer overnight down the Potomac to Old Point Comfort, Va., where they will leave the boat. Thence, by way of Jamestown and Yorktown, they will proceed to Williamsburg to inspect the restoration work done in this early colonial town. Saturday will be spent at Williamsburg. The party will return in the evening, arriving in Washington on Sunday morning. There will be an all-day excursion to the New York World's Fair on Tuesday, May 21, the Eighth American Scientific Congress Day.

RECENT DEATHS AND MEMORIALS

DR. RODNEY H. TRUE, emeritus professor of botany at the University of Pennsylvania, died on April 8 at the age of seventy-three years.

DR. CYRUS ADLER, since 1908 president of Dropsie College, Philadelphia, previously from 1892 to 1905 librarian of the Smithsonian Institution, died on April 7 at the age of seventy-six years.

JAMES A. REYNOLDS, professor of engineering at Tufts College, with which he was associated for twenty-two years, died on April 6 at the age of fifty-three years.

DR. CHARLES K. FRANCIS, consulting petroleum technologist and chemist, editor of *The Oil and Gas Journal*, died suddenly on March 25 in his sixty-fifth year.

CHARLES REID BOGGS, electrochemist and vice-president and general manager of the Simplex Wire and Cable Company of Cambridge, Mass., died on April 1 at the age of fifty-six years.

DR. JOHN LOVETT MORSE, emeritus professor of pediatrics at the Harvard Medical College, died on April 3 in his seventy-fifth year.

DR. JOSHUA ROSETT, professor of neurology at the College of Physicians and Surgeons of Columbia University, died on April 4 at the age of sixty-five years.

PROFESSOR E. MARAGLIANO, emeritus professor of clinical medicine in the University of Genoa, has died at the age of ninety-one years. He founded the first Italian institute for scientific and practical studies on tuberculosis.

Nature records the death of Professor W. C. Brøgger, rector of the University of Oslo, a foreign fellow of the Geological Society of London, on February 17 at the age of eighty-eight years, and of Professor Károly Schaffer, emeritus professor of neurology and psychiatry in the University of Budapest, at the age of seventy-five years.

A MEETING of the John Burroughs Association to celebrate the birthday of John Burroughs has been held at the American Museum of Natural History under the presidency of Dr. Clyde Fisher. The John Burroughs Medal for 1940, which had been awarded to Arthur Cleveland Bent, was presented *in absentia* owing to his illness.

THE memory of Thomas A. Edison was honored on April 1 by the city of Stratford upon the occasion of the Canadian premiere of the motion picture "Young Tom Edison." A civic plaque was unveiled in the Canadian National Railways station, erected upon the site of the old Grand Trunk depot where Edison

worked as a railway telegrapher three quarters of a century ago. The plaque was unveiled by Dr. J. W. Browning, of Exeter, now ninety-five years old, who once worked with Edison.

SCIENTIFIC NOTES AND NEWS

AT the annual congress of the American College of Physicians, which opened at Cleveland on April 1, the John Phillips Memorial Award for "outstanding work in internal medicine" was presented to Dr. René J. Dubos, of the Rockefeller Institute for Medical Research, New York. His investigations, according to the official citation, "have established a new principle of great importance in the study of the chemistry of living cells and of chemotherapeutic substances."

THE John Hunter Medal and Triennial Prize has been awarded by the Royal College of Surgeons of England to Dr. Lionel Ernest Howard Whitby for his research work in "bacteriology with special reference to the sulphonamide compounds."

AT the Cleveland congress of the American College of Physicians, Dr. James D. Bruce, of the University of Michigan, who was chosen president-elect last year, was inducted into office, succeeding Dr. O. H. Perry Pepper, of Philadelphia. Dr. Roger I. Lee, of Boston, formerly professor of hygiene at the Harvard Medical School, was chosen president-elect.

PROFESSOR JOHN PAUL NAFE, head of the department of psychology of Washington University, St. Louis, has been elected president of the Southern Society for Philosophy and Psychology.

DR. WILMER SOUDER, chief of the dental research laboratory at the Bureau of Standards, was elected president of the International Association for Dental Research at the recent convention in Philadelphia.

SIR ROBERT HUTCHISON was reelected on March 18 president of the Royal College of Physicians, London.

DR. WINTERTON C. CURTIS, professor of zoology at the University of Missouri, has been appointed dean of the College of Arts and Science. He has been acting dean of the college since September 1.

DR. ERNEST D. WILSON, formerly president of the Zialite Corporation, New York, N. Y., has been appointed head of the department of chemical engineering and chemistry of the Worcester Polytechnic Institute.

FELIX MORLEY, editor of *The Washington Post*, will become president of Haverford College in September. He is the son of the late Dr. Frank Morley, formerly professor of mathematics at the Johns Hopkins University, and the brother of Christopher Morley, the author. Dr. William Wistar Comfort, having reached the age of sixty-five years, will retire in June after serving twenty-three years as president.

DR. ROBERT FRANKLIN POOLE, plant pathologist at the North Carolina State College and chairman of the committee directing graduate instruction, has been elected president of Clemson College, South Carolina.

PROFESSOR KATHERINE CRANOR, of the department of textiles and clothing of the Iowa State College, has resigned because of ill health.

DR. ROYD RAY SAYERS, medical officer in charge of the office of industrial hygiene and sanitation of the U. S. Public Health Service, from 1917 to 1933 chief surgeon and chief of the health and safety branch of the U. S. Bureau of Mines, has been named by Harold L. Ickes, Secretary of the Interior, acting director of the bureau. Dr. Sayers succeeds Dr. John W. Finch, director of the bureau since 1934.

AT a meeting of the trustees of the General Education Board on April 4 new members of the board were elected as follows: Dr. Karl T. Compton, president of the Massachusetts Institute of Technology; Dr. J. R. McCain, president of Agnes Scott College; Dr. Francis T. Spaulding, of the Graduate School of Education of Harvard University, and President Robert Gordon Sproul, of the University of California.

DR. ROBERT E. DOHERTY, president of the Carnegie Institute of Technology, Pittsburgh, Pa., has been appointed a member of the National Aeronautical Committee, succeeding Brigadier General Walter G. Kilner, retired.

DR. ELLIOTT P. JOSLIN, clinical professor of medicine, emeritus, at the Harvard Medical School, will succeed the late Dr. Harvey Cushing as honorary chairman of the Division of Medicine and Public Health of the President's Committee on University Development, which is planning to secure additional endowment for the Medical School at Yale University.

AT the annual meeting of the American Philosophical Society, which meets in Philadelphia on April 18, 19 and 20, Dr. Dayton C. Miller, honorary professor and acting head of the department of physics of the Case School of Applied Science, on the evening of April 18 will deliver a lecture entitled "The Pipes of Pan, Old and New." The Penrose Memorial Lecture will be given on Friday evening, April 19, by Archibald MacLeish, librarian of Congress. He will speak on "Writers and Scholars." Both lectures will be

given in the hall of the society in Independence Square at 8:15 P.M. They will be followed in each case by a reception.

DR. THOMAS PARRAN, Surgeon-General of the U. S. Public Health Service, gave the fourteenth William Thompson Sedgwick Memorial Lecture of the Massachusetts Institute of Technology on Thursday, April 11. The subject of the lecture was "Nutrition and the Nation's Health."

DR. JOSEPH T. WEARN, professor of medicine at the School of Medicine of Western Reserve University, will deliver the seventh Harvey Society Lecture of the current series at the New York Academy of Medicine on April 18. He will speak on "Morphological and Functional Alterations of the Coronary Circulation."

DR. PAUL DUDLEY WHITE, lecturer in medicine at the Harvard Medical School and physician of the Massachusetts General Hospital, gave on April 4 the Hermann Michael Biggs Memorial Lecture at the New York Academy of Medicine. The subject of the lecture was "Heart Disease—A World Problem."

DR. H. H. SHELDON, managing trustee of the American Institute of the City of New York, will present the academy address at the fifty-fourth annual meeting of the Iowa Academy of Science to be held at Cornell College, Mount Vernon, on April 19 and 20. His subject will be "Television."

DR. ROBERT CUSHMAN MURPHY spoke on March 30 at an Inter-American Fiesta sponsored by the American Museum of Natural History and the Courier Service of New York in honor of citizens and friends of the Republics of Colombia, Peru and Chile. His subject was "Nature and Man on South America's West Coast."

PROFESSOR R. A. DALY, of Harvard University, and Professor Douglas Johnson, of Columbia University, were guest speakers in the department of geology of the University of Kansas during the current semester. Professor Daly spoke on "Submarine Canyons" on February 17. Following the lecture there was an informal luncheon and discussion for staff members and graduate students. Professor Johnson presented three lectures, entitled "Topography and Strategy in the Present European War," "Mysterious Craters of the Carolina Coast" and "Is the Atlantic Coast Sinking?," on March 28 and 29. The second of the three lectures was sponsored by Sigma Xi.

PROFESSOR JAMES CHADWICK delivered the tenth Joule Memorial Lecture before the Manchester Literary and Philosophical Society on March 19. His subject was "New Applications of Physics to Medicine."

THE thirty-fifth anniversary of the founding of the Milbank Memorial Fund was celebrated at the New York Academy of Medicine on the evening of April 3. Dr. Frederick P. Keppel, president of the Carnegie Corporation, made the principal address, speaking on philanthropic foundations. Professor C.-E. A. Winslow, of the Yale University School of Medicine, introduced Dr. Keppel. Frederick Osborn, research associate in anthropology of the American Museum of Natural History, chairman of the section of the fund on population trends and programs of social welfare, spoke on population trends in the United States.

THE dedication exercises of the new W. K. Kellogg Foundation Institute of Graduate and Postgraduate Dentistry at the University of Michigan were held in connection with the annual homecoming of dental alumni of the university on April 3 at a formal university convocation. A monument to Dr. Willoughby D. Miller, an alumnus and a former dean of the School of Dentistry, was unveiled. The memorial statue will stand at the point where the old dental building is joined to the new $500,000 Kellogg Institute building. This building was presented to the university by Dr. Emory Morris, associate director of the W. K. Kellogg Foundation of Battle Creek. Following the formal acceptance of the structure by President Alexander G. Ruthven, responses were made by Dr. R. W. Bunting, on behalf of the School of Dentistry; by Dr. Paul H. Jeserich, director of the institute, on behalf of the department of graduate and postgraduate dentistry; by Dr. Clarence S. Yoakum, on behalf of the Graduate School; by Thomas G. Reid, of Chicago, on behalf of the Public Works Administration, and by Dr. Oliver W. White, Detroit, on behalf of the alumni.

AN appropriation of $1,150,000 has been made by the Rockefeller Foundation to the University of California to construct a cyclotron of 4,900 tons, under the supervision of Dr. Ernest O. Lawrence. The machine will produce energies in excess of 100,000,000 volts. The gift is contingent upon the raising of the sum of $250,000 by the university.

MARSHALL FIELD, 3D, has donated to the University of Chicago property in the Loop which he values at $1,000,000. Fifty years ago his grandfather, Marshall Field, presented ten acres of land, which provided the original site for the present university.

THE eighteenth annual meeting and scientific session of the Academy of Physical Medicine will be held at Richmond, Virginia, on April 24, 25 and 26, under the presidency of Dr. Harold D. Corbusier, Plainfield, N. J.

THE American Association of Physics Teachers will meet from June 26 to 30 at the University of Washington, Seattle, in connection with the meeting of the

American Association for the Advancement of Science. Professors A. A. Knowlton, Reed College, and F. A. Osborn, University of Washington, are in charge of the program and local committees, respectively. The Meany Hotel will be headquarters for the meeting.

THE fifth summer colloquium for college physicists will be held on June 13 to 15 at the State University of Iowa. There will be an exhibit of new laboratory experiments, one day devoted to consideration of the first course in physics for non-technical students, and a discussion of applied subjects in the oil and radio industries and in music.

THE twenty-fifth annual meeting of the American Association of Industrial Physicians and Surgeons, together with the first annual meeting of the American Industrial Hygiene Association, will be held at Hotel Pennsylvania, New York City, on June 4, 5, 6 and 7. The convention will be intensively devoted to the problems of industrial health in all their various medical, technical and hygienic phases, with particular stress on prevention and control of occupational hazards. Important programs have been prepared, and technical and scientific exhibits will be a feature of the convention. The dinner on Thursday evening, June 6, will be the occasion of the presentation of the Wm. S. Knudsen award for the year of 1939–40. All who have an interest in these phases of industrial health, including industrial hygienists, safety engineers, chemists, plant engineers and personnel managers, are urged to attend.

THE Field Conference of Pennsylvania Geologists will be held in New Jersey on May 30 and 31 and June 1, with headquarters at Cochrane House, Newton, N. J. There will be an all-day excursion to Culver's Gap and to McAfee Quarry on Thursday, and on Friday to the Franklin ore deposits, to Mine Hill, Dover, and if time permits to Muggy Hollow. It is planned to spend the night at New Brunswick. On Saturday a study will be made of the stratigraphy of the coastal plain, with a luncheon at Cliffwood.

APPLICATIONS for grants from the Cyrus M. Warren Fund of the American Academy of Arts and Sciences should be received by the chairman of the committee, Professor James F. Norris, Massachusetts Institute of Technology, Cambridge, Mass., not later than May 1. Grants are made to assist research in the field of chemistry. On account of limited resources, grants to an individual are seldom made in excess of $300. The application should be accompanied by an account of the research to be undertaken, a statement of the sum requested and the manner in which the money is to be expended.

THE office of the secretary of the American Institute of Chemical Engineers was moved to The Chemists' Club Building, 50 East 41st Street, New York, on April 1. The membership of the institute has increased from about 1,500 members to 2,400 during the past three years and the quarters in the Engineering Societies Building had become inadequate.

TWO new scholarships to aid students in the Medical College in New York were recently established by the Trustees of Cornell University. The Jeremiah S. Ferguson Scholarship Fund of $5,000 memorializes a member of the original Medical College Faculty, secretary of the college since 1914, who died on June 30, 1939. The income of approximately $200 a year will be awarded annually to outstanding students in the third and fourth years in need of financial aid. An anonymous gift of $10,000 endows the Charles R. Stockard Scholarships, in memory of Dr. Stockard, who had been a member of the faculty since 1906 and who died on April 17, 1939.

ACCORDING to an Associated Press dispatch, Homer Cummings, the former Attorney-General, has established a clinic in George Washington University Medical School as a memorial to the late Mrs. Cummings. The clinic, the only one of its kind in the country, will investigate high blood-pressure and concomitant ailments.

Nature writes that the *Anglo Soviet Journal* "has been started with the purpose of supplying 'the more scientifically skilled and specialized workers in the British Commonwealth with a regular flow of information, accurate and reliable, on the progress and developments that are being realized in the U.S.S.R., in their own field, the field which they understand best.' The first issue is largely devoted to accounts of exhibitions, particularly of the great Agricultural Exhibition held in Moscow last summer, which was unquestionably the most magnificent effort of its kind the world has ever seen."

DISCUSSION

A TIGER SHARK AND A BASKING SHARK RAMMED BY STEAMERS

THAT the great sluggish whale shark, entirely unafraid of ships, should occasionally be rammed by steamers should arouse no incredulity. And thanks to the invaluable help of the U. S. Hydrographic Office, I have recorded 12 such cases between 1922 and 1938. These have all been brought together in an inclusive article, now seeking publication. One of these cases is of a whale shark (*Rhineodon typus*) rammed near the Isle of Perim in the Strait of Bab el-Mandeb by the Dutch steamship *Johan van Oldenbarnevelt* in 1933.

Dr. H. C. Delsman was on board, saw the fish and made the first record in 1934. Later I secured further data and published them, and for the general paper I secured a splendid photograph of this rammed *Rhineodon*.

A TIGER SHARK RAMMED OFF PERIM ISLAND, RED SEA

In 1936, Major Stanley Flower sent me a clipping from a London paper which read as follows: "Finding her speed reduced by a 25-foot tiger shark impaled on her bow, the 10,786-ton Union-Castle liner *Landaff Castle* had to stop off Perim, the coaling station in the [mouth of the] Red Sea, to remove the shark." In the light of the experience of the *Johan van Oldenbarnevelt* off this very island and of another steamer off Socotra Island nearby in ramming whale sharks, I naturally thought this a whale shark and not a tiger. However, through the help of the U. S. Hydrographic Office, I got in touch with Captain G. H. Gogden, master of the *Landaff Castle*, who kindly gave me full data about this interesting matter.

Where and when the fish was impaled is uncertain, but it was first noticed when close to Perim Island. The shark was rammed just behind the right pectoral fin. The head on one side the bow was turned so that the mouth and white under parts could be seen. The hinder part of the body on the other side of the stem showed the stripes. The exact position of the head and tail on the bow plates was carefully noted and, when the ship docked at Mombasa, these were measured and it was shown that the shark must have been from 35 to 37 feet long. An attempt was made to photograph the fish, but the bow waves prevented this. The ship was stopped and backed, whereupon the shark sank, accompanied by a flock of other sharks which attacked it as it went out of sight.

Captain Gogden knows both the whale shark and the tiger. His shark had a pointed snout with the mouth underneath and having "the form of a curve or half-moon." The body was dark brown, particularly in the region of the stripes. These stripes were wide and extended diagonally from top or left to bottom or right. There are in the Indian Ocean and Red Sea two striped sharks—*Rhineodon*, with terminal mouth and vertical narrow stripes, and *Stegostoma tigrinum*, with mouth and coloration as noted. From this it seems that Captain Gogden's shark was surely the Indian Ocean tiger shark, *Stegostoma tigrinum*. As to the size it attains, I can find little. It is recorded up to 15 feet but must grow longer, since in Ceylon it has been confused with the whale shark (well known there) which grows to 30 or 40 feet.

THE BASKING SHARK, *Cetorhinus maximus*

Whale and tiger sharks are warm-water dwellers, but the basking shark is a cold-water fish. However, *Cetorhinus* grows large—30, 40 or 50 feet—rivalling *Rhineodon* in length. But *Cetorhinus* has a pointed snout and is small forward, whereas *Rhineodon* has a broad blunt head and is tadpole-shaped. *Cetorhinus* is rather sluggish in movements, and here follows an account of an individual rammed by a steamer. This is contained in a clipping from a Norwegian newspaper (dated Oslo, August 6, 1935) kindly sent to me in 1935 by Dr. C. H. Townsend, then director of the New York Aquarium.

> On a return trip from the North Cape, the Norwegian ship *Stavangerfjord* is reported to have rammed a giant shark [Brugde, the Norwegian name for the basking shark]. The shark hung fast to the bow and the vessel had to be slowed down in the endeavor to set it free. The crew attempted to get the fish aboard, but failed through lack of proper tackle. The shark eventually got free from the stem while the ship was moving at slow speed. The head of the fish was badly damaged. The shark was estimated to be 25 feet long.

Here then in addition to the 12 whale sharks recorded as rammed by ocean vessels, we have two others, the Indian Ocean tropical tiger shark and the North Atlantic cold-water basking shark. I am unable to ascertain anything about the habits of *Stegostoma*, but all the figures seen show it to be long and lanky, and hence we may presume that it is sluggish in movements. *Cetorhinus* is known to be a slow and deliberate swimmer. This was admirably portrayed on the screen some years ago in the interesting picture "Men of Arran." Hence we must conclude that both these presumed sluggish sharks contributed to their destruction by blundering into the paths of the ocean steamers.

E. W. GUDGER
AMERICAN MUSEUM OF NATURAL HISTORY

APPARENT SPLITTING OF LIGHT FROM FLUORESCENT LAMPS INTO COMPONENT PARTS BY MOVING OBJECTS

MOVING objects illuminated by fluorescent lamps show not only the usually noted stroboscopic effects associated with intermittent flashing light, *viz.*, the appearance of multiple images from moving objects or apparently stationary positions of rotating or vibrating objects, but show in addition an apparent splitting of the incident light into separate colors, depending upon the color characteristics of the lamp. A series of multi-colored images appears when a rod or opaque object is passed across the path of the light. An iron wire or a thin strip of steel made to vibrate in a magnetic field produced by a 60 cycle A.C. current appears as if consisting of two parts. In light from a "daylight" lamp the outer image appears red, the inner image—blue. The same phenomenon is readily observable when such light is viewed through slits in

revolving discs, after the method of Plateau. The relative position of the red and blue bands varies with the direction of rotation. Splitting of light also appears when a triangular faced mirror is made to rotate in the path of the light.

Separation of the incident light varies with the source. A wide degree of separation has been observed when a light divider, consisting of a disc 60 cm in diameter, perforated at the periphery with 60 narrow radia slits, is rotated at a constant speed. Under these conditions "blue" light from the lamp appears to be broken up into a comparatively wide pale blue band and a narrow dark band either dark brown or maroon. Light from the "green" lamp is divided into yellow-green and pale blue bands of nearly equal width. Light from the "daylight" lamp is clearly divisible into orange red and greenish-blue bands, which spread further into merging bands discernible as purple-blue-green-yellow-orange and red.

There are several conceivable explanations for the apparent separation of light into its component parts. These possibilities include accounts based either upon subjective or psychological factors or upon objective physical phenomena. In the former instance the apparent splitting might be attributed to a variation in the threshold of stimulation of the end organs of the eye by alternating light as in Benham top wherein alternate black and white stimuli give rise to the sensation of color. Obviously this possibility might be tested by color photography. Since a color pattern comparable to the one described has been reproduced on a Dufa film by exposure for 30 minutes to light reflected from the rotating wheel of an electric clock the phenomena can not be explained upon a subjective basis and it is necessary to consider objective physical factors.

These chromogenic phenomena do not appear when moving objects are illuminated by light from ordinary incandescent lamps or in sunlight.

This leaves the nature of the light produced by the fluorescent lamps as a possible basis for the phenomena. The mechanism of operation of the lamp suggests the possibility that there are differences in the time intervals of emission of light of various wave-lengths. It may be assumed that the mercury discharge appears first, and this in turn stimulates or activates the fluorescent coating. Characteristic wave-lengths of the latter are then emitted. This cycle of color emission is repeated for each electrical cycle. Moving objects merely provide an optical means of separating these alternate flashes. Under ordinary conditions the rapidity of the flashes obscures the presence of the rapidly alternating production of colors. High-speed color photography synchronized to the various parts of the cycle could definitely determine the correctness or incorrectness of this view. In the absence of facilities for making this direct test an alternative trial mimicing the postulated conditions was carried out. A disc with alternate red and blue segments was rotated while illuminated by light from an incandescent lamp. When viewed through a slit in a second stationary disc a composite of the red and blue appeared. When the "analyzing" disc was rotated alternate flashes of red and blue were evident. While lacking a crucial test, the foregoing considerations make it appear that alternate flashes of light of various wave-lengths is the most probable explanation for the apparent splitting of the light of fluorescent lamps into component colors by moving objects.

C. WESLER SCULL
CHARLES G. GROSSCUP
E. G. WITTING
ABINGTON MEMORIAL HOSPITAL,
ABINGTON, PA.

BIOGRAPHY OF DR. WILLIAM H. PARK

I AM at work upon a biography of Dr. William Hallock Park, the late director of the New York City Board of Health Laboratories. Any assistance rendered, in the form of the loan of letters, anecdotes or other memorabilia, will be gratefully received, and due acknowledgment given. Reasonably prompt return of letters, etc., is insured.

WADE W. OLIVER
THE WILLIAM HALLOCK PARK LABORATORY,
BUREAU OF LABORATORIES,
NEW YORK, N. Y.

QUOTATIONS

THE END OF "DISCOVERY"

WITH this issue *Discovery* has to end. It began at the end of the last war, and endured with some vicissitudes until April, 1938, when it was renovated by the Syndics of the Cambridge University Press. Now, after two years in its new form and six months of another war, they have reluctantly decided that it must end.

It seems a pity. To any of us who have been concerned with the editorial side of *Discovery*, it is a personal loss to see it go; and we believe that will be true of a good many readers. But it is no use repining. Perhaps, after this war, *Discovery* will be started again, or something like it will. The only service which we can perform, while the end of *Discovery* is fresh in our minds, is to put down one or two reflections for the benefit of our possible successors.

Their first task will be to capture a larger public than *Discovery* has ever had. If it had been a sound financial proposition, it would not have stopped now; it struggled all through its existence, and though in its new form it gained twice as many readers and four times as many subscribers, it was still a long way from paying for itself.

Now that means something: it means something, even if one thinks that good books should be published, irrespective of the money they make or lose. It means either that the public interested in the movement of science is actually rather small or else that it has not yet been properly provided for.

It is hard to believe that the public anxious to read the news of science is really quite small. Perhaps one exaggerates its potential size because of the zest and enthusiasm of so many of its members. It was one of the most pleasant experiences in editing *Discovery* to read letter after letter from readers, full of fresh, original interest. To them, science was something alive, part of the world's vital culture; it is difficult to believe that they form only a small fraction of intelligent people in the world to-day.

If they do not, then the others have not been reached. If that is so, a share of the responsibility rests on the editors who have tried to reach them. Where have we failed?

One gets a good many opinions. They are usually strong, because editing is a job upon which a surprising number of people hold unexpectedly violent views. The two most frequently represented to *Discovery* exactly contradict each other. The first is, that the general level of difficulty has been set much too low. One such critic suggested that all the articles ought to approximate to the standard of "Notes of the Month," *i.e.*, the journal should be made a medium by which professional scientists might keep in touch with fields other than their own. Some critics wanted the journal mainly given over to completely detailed articles suitable for students working for their degrees. And a sort of off-shoot of this view (with a pronounced tinge of dialectical materialism) required articles of that standard, but chosen in order to stress the relation between science and technology.

These critics may be right. But they would have to convince another band, which maintained with equal certainty that the level of difficulty was kept much too high and that the proper work of such a journal was to provide articles of the kind of our "Invitations to Knowledge."

It was our view that both these opposing schools of thought were much too doctrinaire, and that the journal could, and should, contain some articles to interest professional scientists, and others which could be read easily by a child at school. The journal, in fact, was popular among serious scientists, and we were proud of that popularity. Perhaps we leaned too much that way. At any rate, this can be said: If *Discovery* had continued, its general level would have become gradually easier rather than harder. That seemed, on balance, to fit it better for its proper purpose.

Its proper purpose would also have had to be limited. It has been called "a popular journal of knowledge"; regretfully we admit that that is asking too much for any journal in this heterogeneous world. Not many people are now interested in the world entire, and perhaps *Discovery* suffered through attempting to be too broad (although, of course, it was also criticized for being too narrow). If it had continued, we should have concentrated more on the fundamental sciences.

So, in short, our experience would have led us to make *Discovery* narrower in scope: simpler in manner (though finding writers who can simplify science truly is getting no easier).

All we hope now is that before long the same job will be tried again and carried farther.

The Editor of Discovery in the issue for March, 1940

SCIENTIFIC BOOKS

RECENT BOTANICAL BOOKS

Botany. By WILLIAM J. ROBBINS and HAROLD W. RICKETT. xii + 658 pp. 440 figs. Third edition. New York: D. Van Nostrand Company. 1939. $3.75.

IT is rather appropriate that Part I of this text should be entitled "The Living Plant," since, more than other somewhat similar books, this treatise emphasizes the physiological and hence the living aspects of plant life. Not departing very far from the traditional in its sequence of presentation, this volume is concerned first with the growth, structure, responses, reproduction and inheritance in the higher plants; in Part II the groups in the plant kingdom are considered in evolutionary sequence.

Both portions of the book do ample justice to the subject-matter. Forty pages and thirty-six figures are devoted, for example, to the structure and functions of stems. Other organs are treated with similar thoroughness. Likewise in the discussion of the plant groups there is attention to detail. In the angiosperms, for instance, we are introduced to sixteen different orders, starting with the Ranales.

In view of the large number of excellent texts in botany, the mere compilation and digestion of the general subject-matter of the science into book form can

hardly be considered any longer as an outstanding achievement. Each new edition or book should consequently be appraised, partly at least, on the basis of the presence of outstanding features. These are fortunately not lacking in "Robbins and Rickett."

It is consoling, for instance, to see that Dutrochet—"the forgotten man of the cell theory"—is given credit along with Schleiden and Schwann. Two pages are devoted to "tank culture," and together with specific directions there is the wise admonition that "there is considerable likelihood that inexperienced individuals attempting to raise plants in tanks will be disappointed." Vitamins, a special forte of the senior author, are ably discussed. The possible danger due to selenium of wheat coming from certain sections of the country and used as a food is pointed out.

Since the book is intended primarily "for general students as part of an education which all should have," rather than for the training of professional botanists, the inclusion of the more philosophical and striking aspects of the science is not only justified but desirable. There is, for example, a chapter on "The Nature of Life," in which vitalism and mechanism, the scientific conception of life and even the limitations of science are discussed in unimpassioned and wholly unbiased terms. In accordance with the more popular aspects of the book are statements such as the warning that our "energy-dissipating civilization" is leaning heavily on the "'bottled sunlight' of coal and petroleum" and can not continue to do so indefinitely. Similarly, there is also a full-page illustration of *Amorphophallus titanum*—the "largest known inflorescence." The illustrations as a whole are very adequate and mostly original.

This is a rather large volume, and the student is introduced, in separate chapters, to "The Origin of Life," "The Evolution of Life" and to "The Distribution of Plants on the Earth." In the chapter on evolution, the importance of geographical isolation, in the Hawaiian Islands, is happily stressed.

There are nine pages of references and thirty-six pages of questions for review and discussion with ample food for thought for those inclined to masticate.

Floral Morphology. By E. R. SAUNDERS. Vol. 2. xiv + 133–609 + vii pp. 7–48 figs. Cambridge: W. Heffer and Sons. 1939. 10s. 6d.

IN the companion volume (1), published two years ago, the thesis is presented and defended that the syncarpous gynoecium is made up of two kinds of carpels, sterile and fertile. Evidence for such "carpel polymorphism" was first suggested by a study of the *Cruciferae,* and it has since been applied by the author in an interpretaiton of the pistils of many other families.

It is pointed out in the introduction to Volume 2 that "the fundamental feature of the whole vascular scheme is the departure from the central axial cylinder of bundles corresponding in number and in their radial disposition with the number and arrangement of the floral members," although there may be modifications. The presence of three bundles in a flower part is said to be correlated with the branching of the midrib bundle and is not considered to be of particular significance.

The principles of flower interpretation here presented are then applied in the analysis of representatives of 190 families of angiosperms, of which 151 are to be found in Volume 2. One or more (often several) illustrative types are used for each family. While interest centers mostly in the carpels and their interpretation, much additional and valuable information on the flower characters of the families and of the selected types is also given, dealing with the external form, the internal architecture and with their interrelationships.

In the appendix, entitled "A Century's Challenge to Orthodoxy in Ten Chapters, with Preface and Epilogue," the author quotes the statements of numerous previous writers who accepted the view that some pistils, at least, are made up of two kinds of carpels.

Although there has been criticism of such wide application of the theory of carpel polymorphism, it is well worth while to have all this material brought together, in fairly concise form, for future discussion and study.

Basic Course in Botany. By RAYMOND J. POOL. v + 654 pp. 541 figs. Boston: Ginn and Company. 1940. $3.75.

THIS volume is organized on the general plan followed in the majority of our larger text-books. After two introductory chapters there is the treatment and discussion of the cell, tissues, and then of roots, stems, leaves, flowers, fruits and seeds. The material presented is more complete than that in most text-books—248 pages in all being devoted to these aspects of the plant.

The next part of the book deals with the groups in the plant kingdom—"The Nature of the Plant World." The algae and fungi are taken up in considerable detail. The angiosperms are also by no means neglected, since twenty-two families of the dicotyledons and eight of the monocotyledons are discussed at some length. In the presentation of the material on these higher flowering plants, considerable emphasis is fortunately placed upon the economic aspects. Over a hundred pages are devoted also to chapters on environment, vegetation regions, plant diseases, and variation, heredity and evolution.

Among the more unusual features of this text is the large number of diagrams illustrating the life cycles

of various members of the plant kingdom. These should facilitate the mastery of this aspect of the subject which is often a stumbling block to the neophyte. Many of the numerous illustrations are original, and a considerable number have been borrowed from the older authors, such as Hooke, Grew, Linnaeus, Sachs, Baillon, Kerner, Kny and others. It is surprising that so many of these older figures can be used to advantage in a new book on botany. Both the illustrations and numerous passages in the text emphasize the phases of the subject that are more striking or more general in their appeal, such as the occurrence of gigantic puffballs (one weighing sixty-one pounds) and the staggering figures on reproduction and size (or lack of it) in the bacteria.

"Basic Course in Botany" is no child's play. It is a copious assignment for a one-year introduction to the subject, especially for college freshmen, though no more so than many other similar treatises.

The author writes with a facile pen, and while a volume such as this can hardly be termed "easy reading," it is often rather pleasant. He finishes his task with the optimistic prophecy that "countless forms more interesting, useful, and beautiful than any that have yet appeared may readily grace those new scenes of nature's unending pageant of life."

Edible Wild Plants. By OLIVER PERRY MEDSGER. xv+323 pp. Illustrated. New York: The Macmillan Company. 1939. $3.50.

As our civilization becomes more and more complex and specialized and in many ways more artificial, contact with the good earth and association with its humbler citizens seems to be less and less frequent. Even in the clan of broad-footed, leather-cheeked trampers, there is little real knowledge of the edibility or palatability of the great majority of our wild plants. Until the present volume appeared, it was exceedingly difficult to locate such information.

In "Edible Wild Plants" much information is assembled in orderly and usable fashion. Ninety pages, for example, are devoted to wild fruits which can be eaten, either raw or cooked—the sugarberry, for instance, eaten raw; barberry, used in preserves and jellies; the fruit of the may apple, edible when quite ripe, especially if it is consumed with discretion; the red currant, used in pies and jellies; the gooseberries, berries of the shadbush, eaten either raw or cooked; the creeping snowberry (*Chiogenes*), the partridge berry, the viburnums and a host of others. In addition there are discussions of edible nuts, from the Rocky Mountain nut pine to the acorns of some of the oaks, which must be properly treated, of edible seeds and seed pods, of salad plants and potherbs, including Irish moss, rock tripe—"an emergency food"—and the unfolding fronds of the bracken, which must be cooked. The young tender leaves even of the skunk cabbage, if deftly and properly handled, may be made "pleasing."

"Edible Roots and Tubers," such as the underground rootstocks of the arrowhead, *Sagittaria,* are considered, as are "Beverage and Flavoring Plants," like the black birch and sassafras, and "Sugars and Gums." There are numerous illustrations, and also "Finding Indices" of edible plants of various parts of the United States.

This volume is no mere tabulation; it is replete with intimate information on the characteristics and qualities of many of our wild plants, interestingly presented by an author who is obviously very familiar with them. It will be especially appreciated by those who wish to temper botanical knowledge with practical wisdom.

Poisonous Plants of the United States. By WALTER CONRAD MUENSCHER. xvii+266 pp. 75 figs. New York: The Macmillan Company. 1939. $3.50.

No extensive treatise on the poisonous plants of the United States has appeared in recent years, and the volume under consideration aims to bring together the contributions of the more recent literature and incorporate them into the great body of factual material that has slowly accumulated over a long time.

In Part I certain general topics are taken up, such as the chemical nature and properties of the toxic principle in poisonous plants and its physiological action, as well as the conditions under which poisoning occurs. There are also brief general discussions—too brief, perhaps—of plants causing dermatitis, of plants like buckwheat that cause photosensitization in certain animals, of plants causing hydrocyanic acid poisoning, of plants like some of the species of *Astragalus, Oonopsis, Stanleya* and others which may become poisonous through the absorption of selenium from the soil, and finally of plants which cause mechanical injury.

The second portion of the book—comprising the great bulk of the volume—gives the poisonous plants of the United States, arranged according to families. About 400 species in sixty-eight families are considered, beginning with the ferns (*Polypodiaceae*) and ending with the *Compositae.* In many cases the species are taken up under the following headings: Description, Distribution and Habitat, Poisonous Principle, Conditions of Poisoning, Symptoms and Treatment. Most of the genera and many of the species are illustrated with clear line drawings.

This volume is a convenient compilation, in compact form, of a mass of material, much of which is of interest to the general botanist as well as to the layman. In assembling such data with reference to the more recent contributions, it fills a distinct hiatus.

EDWIN B. MATZKE

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REPORTS

REPORT OF THE BANTING RESEARCH FOUNDATION FOR THE YEAR 1938–1939

THE annual meeting of the trustees was held late in January, 1940, and at this meeting was submitted the Annual Report of the Honorary Secretaries. This revealed that twenty grants had been made during the year. Slightly less than half of the foundation's income was placed at the disposal of Sir Frederick Banting in the Department of Medical Research, University of Toronto, to finance research of his choice. The remainder of the foundation's income was distributed to nineteen applicants in different parts of Canada, whose research projects were favorably viewed by the trustees.

It was noted in this report that from the character of the applications being received by the foundation, it was obvious that the modern trend of medical research is increasingly toward learning more about the formation, nature and action of substances which exert physiological effects and which, in deficiency, excess or altered forms, induce pathological states. The relation of this type of research to a better understanding of many of the diseases of middle life which have not yielded to the researches of the Pasteur era was noted.

The fact that the foundation was able in the past year to finance a relatively vast amount of research in relation to its income also received comment. The chief reason for this, it was suggested, is to be found in the fact that there are in Canada many competent research workers who must necessarily spend most of their time in work which provides them with their livelihood, but who can arrange for enough time to carry on either additional research or a research problem if they have funds for technical help and research materials. In the case of these individuals a relatively small Banting grant is frequently the marginal factor in allowing a research problem of a superior quality to be prosecuted.

SUMMARIES OF REPORTS MADE TO THE FOUNDATION BY NINETEEN INDIVIDUALS IN CANADA WHO WERE WORKING UNDER INDIVIDUAL GRANTS WHICH TERMINATED DURING THE YEAR

Dr. W. J. Auger, Department of Pathology, Hospital for Sick Children, Toronto, reports that by using carbon dioxide to stimulate the growth of pneumococci on solid media he has developed a practical means of isolating pneumococci in sputum. He also reports his results with regard to serum therapy and serum plus chemotherapy in lowering the incidence of empyema in Type I pneumonia in children.

Dr. K. W. Baldwin and Dr. A. W. Ham, working in the Department of Anatomy, University of Toronto, report that the epithelium in the respiratory portion of the foetal lung becomes discontinuous in the latter part of pregnancy and that capillaries thereafter form the chief lining of alveoli. They suggest intra-uterine respiratory movements are potent factors in affecting the position and growth of capillaries in the later part of foetal life.

Mr. R. W. Begg, Department of Pharmacology, Dalhousie University, Halifax, reports that he has investigated the sedimentation rate in 164 cases of disease and is making a statistical survey of his results to discover whether there is any correlation between sedimentation rate and the concentration of certain constituents of blood (cholesterol, plasma, proteins, etc.).

Miss M. G. Chapman, working in the Department of Anatomy, University of Toronto, reports that to date she has been unable to demonstrate in tissue cultures growth-stimulating effects of certain hormones comparable with those seen when they are injected into the living body.

Dr. H. B. Collier, Department of Biochemistry, University of Toronto, reports that he has studied the enzymic synthesis of plastein with papain, from both peptic and papain digests of ovalbumin, as well as various factors affecting the synthesis. He also submits further evidence that plastein is a protein.

Mr. B. F. Crocker, Department of Biochemistry, University of Toronto, for the study of digestion in dogs prepared with the type of fistula he devised, is using protein labelled with deuterium in order to distinguish fed from secreted protein.

Dr. G. H. Ettinger, Department of Physiology, Queen's University, Kingston, reports his results with regard to assaying esterase in the human placentae and his experiments in which oestrogens were not found to exert a cholinergic effect on the placentae of common laboratory animals.

Dr. R. D. H. Heard, working in the Department of Biochemistry, Dalhousie University, Halifax, reports the isolation of a new saturated hydroxy-ketone from the neutral fraction of pregnancy urine.

Dr. W. Hurst Brown, working at the Western Hospital, Toronto, reports he has found no correlation between the efficacy of sulfapyridine in bacteriostatic tests and in the treatment of pneumonia. He also reports results of his studies on the absorption, distribution and excretion of administered sulfapyridine in eighty patients.

Dr. E. Kuitunen, working in the Department of Hygiene, University of Toronto, by means of facilities

laced at her disposal by the Hospital for Sick Children, Toronto, has found the incidence of intestinal arasites in Toronto children to be much higher than generally appreciated.

Mrs. H. T. Malloy, working in the University Clinic, oyal Victoria Hospital, Montreal, has investigated ereditary jaundice in rats and has found that it does ot depend upon enhanced hemolysis but rather in the ability of parenchyma liver cells to deal properly ith blood bilirubin, *i.e.*, the hereditary factor concerns arenchyma liver cells rather than haemopoietic tissue.

Dr. D. G. H. Macdonald, working in the Department f Physiological Hygiene, University of Toronto, reports the results of his study with regard to vitamin B eficiency and slow heart rate. It was found that this tter condition was due specifically to lack of vitamin B_1, but that it was not alleviated by B_1 alone; adequate food intake was needed as well.

Dr. D. W. G. Murray and Dr. R. G. MacKenzie, Department of Surgery, University of Toronto, report esults on further experimental and clinical use of eparin. Heparin is shown to facilitate blood-vessel urgery by preventing thrombosis. Its ability to prent thrombosis in thrombophlebitis, as well as its bility to prevent further thrombosis and embolism in ases where it has already occurred was also estabshed.

Dr. B. Rose, University Clinic, Royal Victoria Hospital, Montreal, reports the results of several studies n histamine. The kidney was found to take up most f the histamine injected into the rat's blood stream. idney, however, was found to be devoid of histminase. Adrenalectomized rats were unable to inacvate histamine. Injections of cortin restored their ormal ability to inactivate it.

Mr. E. A. Ryan, working in the Department of Biochemistry, University of Toronto, reports that previously used methods have not been productive in allowing him to isolate and identify a new compound in male urine. New methods have, however, been utilized which promise to be of considerable help in this and similar researches, and already there is indication that a new ketone has been found.

Dr. M. A. Sergeyeva, working in the Department of Physiology, McGill University, Montreal, reports that definite changes occur in the islet cells of the pancreas when the autonomic nerves supplying that organ are cut or stimulated experimentally. She has furthermore found that, under certain experimental procedures of this type, numbers of cells displaying characteristics of both islet and acinar cells appear.

Drs. R. W. I. Urquhart and D. L. Selby, working in the Department of Pathological Chemistry, University of Toronto, report further progress with their study of experimental nephrosis. They have tested the effects of a standard damage to a more or less specific part of the tubule of one kidney with regard to the elimination of many ions in addition to the chlorine ion.

Dr. P. G. Weil, working in the University Clinic, Royal Victoria Hospital, Montreal, has found that normal individuals do not excrete cortin. It was found, however, that cortin was excreted (1) in certain disease conditions and (2) following operations where its excretion reached a peak in four or five days. Studies on the relationship of cortin to surgical shock are in progress.

V. E. HENDERSON
A. W. HAM
Honorary Secretaries

SPECIAL ARTICLES

THE EFFECT OF THIOL COMPOUNDS ON GONADOTROPHINS[1]

CYSTINE and cysteine in protein molecules have therto been regarded as existing in two definite forms —one in which the sulfur-containing groups give the actions for sulfhydryl or disulfide compounds as these e given by the free amino acids and another form which these reactions are not given. Denaturation known to cause the transformation of many nonactive to reactive[2] groups.

It has only recently been recognized that –SH groups of intermediate reactivity occur in both native and denatured proteins. It has also been shown that –SH groups exist which will react with some and not with other reagents.[3, 4, 5, 6] Results here reported indicate that –S–S– bonds of intermediate reactivity may exist in native proteins. This study was done on highly physiologically active proteins—gonadotrophins—which, however, are not chemically pure; analytical data concerning the state of reduction of such mixtures

[1] Aided by grants from the Research Board of the University of California; from the Rockefeller Foundation of ew York and from Parke, Davis and Company of troit, Michigan. Assistance was rendered by the Fedal Works Progress Administration, Project OP -1-08-62, Unit A-5.

[2] The terms "reactive" and "reactivity" are used here only to indicate whether or not the reactions typical for a certain chemical group are given.

[3] J. P. Greenstein, *Jour. Biol. Chem.*, 125: 501, 1938.

[4] M. L. Anson, *Jour. Gen. Physiol.*, 23: 239, 1939.

[5] A. K. Balls and H. Lineweaver, *Nature*, 144: 513, 1939.

[6] M. L. Anson, *Jour. Gen. Physiol.*, 23: 321, 1940.

of proteins would therefore appear to be of little value.[7] As has previously been reported, pituitary gonadotrophins are inactivated by cysteine.[8] In the present study the degree of inactivation was therefore used to estimate the extent to which the reaction between cysteine and the protein had proceeded. As Table I shows, solutions of 1 mg per cc of various gonadotrophins were almost completely inactivated when treated with a 40-fold amount of cysteine for 2 days at room temperature and pH 7.8; while none of these gonadotrophins was inactivated at concentrations below 0.1 mg per cc under otherwise identical conditions. Nevertheless, if such dilute mixtures of gonadotrophins with cysteine or thioglycolic acid were permitted to stand for longer periods of time or at higher temperatures, marked inactivation resulted. It must be noted that no inactivations were observed in control solutions kept under the same conditions but without the reducing agent. It has been observed that cysteine treatment in 40 per cent. urea solution causes a very much more rapid inactivation of gonadotrophins than that in aqueous solution under otherwise identical conditions.[9] This observation is in good agreement with the established fact that the denaturation of many proteins causes an increase in the reactivity of -SH, -S-S- and other groups.

From these experiments it appears that groups which are essential for the activity of all gonadotrophins thus far studied are affected by these thiol compounds. Since no protein groups besides -S-S- bonds have been shown to react with such compounds, the assumption appears justified that the reduction of certain of these bonds causes the observed inactivation of gonadotrophins. The rate of this reaction is unusually slow, and under the specified conditions the attainment of equilibrium within 48 hours depends on the concentration of the reacting substances. It must be noted that our previous conclusion[8] that as regards their reaction with thiol compounds, a difference exists between the gonadotrophins of pituitary as contrasted with those of chorionic origin can not now be maintained. The former conclusion was drawn before full realization of the importance of protein concentration in these reactions. It may be repeated that thiol com-

[7] Such data are being collected in a similar study of a pure protein hormone (mammotrophin).

[8] H. Fraenkel-Conrat, M. E. Simpson and H. M. Evans, *Jour. Biol. Chem.*, 130: 243, 1939.

[9] The commercial detergent, Duponol PC, which was observed by Anson (footnote 4) to resemble urea in its denaturing effect on proteins, did not appreciably increase the rate of cysteine inactivation of these hormones.

TABLE I

Gonadotrophine	Reagent*	Reaction: Protein mg/cc	Reaction: Time days	Reaction: °C.	Solvent	MED† mg
Pituitary FSH (IVF20B)	.....	0.025	2	22	phosphate buffer (pH 7.8)	0.02
" " "	cysteine	0.5	2	22	" " "	0.15
" " "	cysteine	0.05	2	22	" " "	0.03
" " (IVF28A)	.....	...	..	..	dialysed solution	0.015
" " "	.....	0.05	5	22	phosphate buffer (pH 7.8)	< 0.03
" " "	cysteine	1.0	5	22	" " "	> 0.25
" " "	cysteine	0.05	5	22	" " "	0.05
" " "	.....	0.05	2	40	" " "	< 0.03
" " "	cysteine	0.05	2	40	" " "	> 0.15
" " (IVF28B)	.....	0.05	2	22	40 per cent. urea (pH 7.8)	0.015*
" " "	thioglycolic acid	0.05	2	22	" " " " "	> 0.05*
Chorionic (Antuitrin S)	.....					0.005
" "	cysteine	1.0	2	22	phosphate buffer (pH 7.8)	> 0.1
" "	cysteine	0.05	2	22	" " "	0.007
" "	.....	0.05	1	22	40 per cent. urea (pH 7.8)	0.015
" "	cysteine	0.05	1	22	" " " " "	> 0.09
Teratoma testis urine	.....	1.0	2	22	phosphate buffer (pH 7.8)	0.0015
" " "	cysteine	1.0	2	22	" " "	0.1
" " "	cysteine	0.1	2	22	" " "	0.0015
" " "	cysteine	0.05	2	22	" " "	< 0.0025
Pregnant mare serum (Gonadin)	.....	0.25	2	22	phosphate buffer (pH 7.8)	0.015
" " "	cysteine	1.0	2	22	" " "	0.25
" " "	cysteine	0.05	2	22	" " "	< 0.025
" " "	.....	0.05	9	22	" " "	<< 0.025
" " "	cysteine	0.05	9	22	" " "	> 0.15
" " "	.....	0.1	1	0	" " "	0.015
" " "	thioglycolic acid	0.1	1	0	" " "	0.015
" " "	thioglycolic acid	0.1	1	22	" " "	0.05
" " "	.....	0.1	1	40	" " "	0.015
" " "	thioglycolic acid	0.1	1	40	" " "	0.3

* Of the reducing agents a 40 fold of the protein is used throughout.

† With the exception of those marked with an asterisk which were done in hypophysectomized rats all standardizations were done in normal immature rats. 1 unit of IV F 20B was contained in 0.004 mg of IV F 28A and IV F 28B in 0.006 mg as measured by our routine test for FSH fractions in hypophysectomized rats or by augmentation with chorionic gonadotrophin.

ounds decrease or destroy the potency of all gonado-rophins thus far investigated.

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THE SYNTHESIS OF PHOSPHOPYRUVIC ACID ON OXIDATION OF LACTIC ACID

THE formation of pyruvic acid from phospho-yruvic acid, and its further conversion into lactic cid, are well-studied stages of the anaerobic decom-osition of carbohydrates, whereas the reversal of hese reactions has not yet been fully investigated.*

It is known that lactic acid on oxidation yields yruvic acid, whose further course of aerobic decom-osition is known. We have established that pyruvic cid produced by the oxidation of lactic acid can be hosphorylated, giving rise to phosphopyruvic acid. he synthesis of phosphopyruvic acid has been effected n minced muscle tissue by adding to it sodium lactate ith a good supply of oxygen. Along with the syn-hesis of phosphopyruvic acid there is a decrease in he amount of inorganic phosphate. The presence of hosphopyruvic acid was recognized by its instanta-eous splitting in the presence of mercury ions, and lso from its splitting by iodine in alkaline medium, iving rise to iodoform and inorganic phosphoric acid. s an example we may report the results of one of our xperiments.

The muscle of a cat was minced by means of cissors. Out of this homogeneous mass the following amples were taken:

Sample A: 20 g of tissue incubated for 90 min. at 0° C. with a good supply of oxygen in 50 cc of 2 er cent. $NaHCO_3$ prepared from m/10 sodium lac-ate + 10 cc H_2O + 40 mg KH_2PO_4 (0.45 mg per 1 g of issue).

Sample B: Prepared as sample A + 0.1 g of NaF.

Sample C: 20 g of tissue incubated for 90 min. at 0° C. in 2 per cent. $NaHCO_3$.

Sample D: Control sample, without incubation. 20 of tissue were placed in a 7 per cent. solution of richloracetic acid.

After the incubation the proteins were precipitated ith 20 cc of 25 per cent. trichloracetic acid. Filtra-ion and analyses were carried out after 20 hours tanding in the refrigerator.

Phosphopyruvic acid is absent in samples C and D. must therefore have been absent from the tissue its preformed state. Nor did it accumulate during e incubation without the addition of sodium lactate d without oxygen supply.

TABLE 1

IN MG OF H_3PO_4 – P PER 1 G OF MUSCLE TISSUE

Samples	H_3PO_4 – P after hydrolysis in nHCL at 100° C.					Decrease of the inorganic H_3PO_4 – P	Amount of H_3PO_4 – P formed on hydrolysis in nNaOH within 30′ (triose-phosphate P′)	Amount of H_3PO_4 – P formed on treatment of the protein-free-filtrate with 2nNaOH and I (phosphopyruvic acid – P + triose-phosphate – P)
	0′	7′	30′	60′	90′			
A	0.56	0.77	0.93	0.98	0.98	0.89	0.02	0.20
B	0.27	0.32	0.38	0.41	0.41	1.18	0.05	0.15
C	1.57	1.63	1.63	1.71	1.71	...	0	0
D	1.00	1.33	1.38	1.38	1.38	...	0	0

Sample A shows a considerable content of phospho-pyruvic acid. The amount of acid actually formed in this sample is much larger than what may be inferred from the figure tabulated, as phosphopyruvic acid is in enzymatic equilibrium with phosphoglyceric acid (according to Meyerhof and Lohmann's[1] data, equilib-rium in enzymic solutions at 20° C. is established at 29 per cent. phosphopyruvic acid and 71 per cent. phosphoglyceric acid). The decrease of the amount of the inorganic phosphate, and the accumulation of phosphate stable toward hydrolysis in nHCL, indicate that phosphoglyceric acid was formed along with phosphopyruvic acid.

The formation of phosphopyruvic acid in sample B is particularly conclusive. It is known that NaF blocks the reaction: Phosphoglyceric acid $\leftrightarrows$ phospho-pyruvic acid. This rules out the possibility of phos-phopyruvic acid being a product of the decomposition of glycogen under our experimental conditions.

In 1924 Embden and his co-workers[2] observed the decrease of inorganic phosphate on incubating a minced muscle tissue in the presence of lactate. They believed the anions of the lactic acid to possess a spe-cific power for inducing the synthesis of hexosephos-phate ("lactacidogen") in muscle. The incorrectness of this early opinion was proved by one of us (D.F.),[3] who found that a muscle tissue yields on incubation in lactate a compound which hydrolyses in nHCL in 30 min. and does not reduce $K_3Fe(CN)_6$. The data now obtained have elucidated the nature of the phos-phoric compound thus produced by a muscle tissue on incubation in lactate.

There are reasons to think that lactate is not the only substrate for the synthesis of phosphopyruvic acid. Evidence of this is afforded by the investiga-tions of Kalckar,[4] who observed the formation of phos-phopyruvic acid in renal tissue on oxidation with malic acid.

* Editor's note: Compare, however, the papers of Mey-hof, Ohlmeyer, Gentner and Maier-Leibnitz (*Bioch. Z.*, 8: 396 (1938) and Green, Needham and Dewan, *Bioch.* 31: 2327 (1937).

1 Meyerhof and Lohmann, *Biochem. Z.*, 273: 60, 1935.
2 Embden and co-workers, *Z. Physiol. Chem.*, 143, 1924.
3 Ferdman, *Z. Physiol. Chem.*, 187: 160, 1930.
4 Kalckar, *Biochem. Jour.*, 33: 631, 1939.

The significance of this process for the production of phosphopyruvic acid by the oxidation of lactic acid, and the mechanism of the phosphorylation, are being studied.

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CHEMOTHERAPY IN EXPERIMENTAL INFECTIONS CAUSED BY STREPTOBACILLUS MONILIFORMIS

STREPTOBACILLUS moniliformis is constantly associated with a pleuropneumonia-like organism[1] which may represent a phase in the life history[2] of the *Streptobacillus moniliformis*. In view of a report that gold compounds are effective against infections produced with certain pleuropneumonia-like organisms in rats and mice,[3] it was considered of interest to see whether or not these compounds would also affect experimental infections induced by *Streptobacillus moniliformis*. Such has proved to be the case.

The intra-abdominal injection of Swiss mice with moderate amounts of virulent young cultures of *Streptobacillus moniliformis* causes septicemia resulting in death, usually in from one to three days. The injection of minute amounts of virulent cultures or moderate amounts of old or attenuated cultures frequently causes arthritis involving one or more joints. The virulence of cultures is subject to fluctuations, so that all therapeutic experiments must be well controlled. The microbes used in these experiments were contained in young cultures grown on veal infusion broth containing 20 per cent. horse serum. Swiss mice weighing approximately 20 gm were used and were found to be more susceptible to the infection than a strain of white mice of mixed origin. The gold preparation used was gold sodium thiomalate (myochrysine), which was administered intramuscularly in one dose, usually at the time of the injection of the bacterial culture. A single dose of 0.25 gm of the drug per kilogram of weight of the mouse, administered at the time of injection of the microbic culture, or twelve hours before or after, was effective in protecting against from 100 to 1,000 times the least amount of culture necessary to cause death in four out of five mice within three days.

Individual experiments consisted in the intra-abdominal injection of a given amount of bacterial culture into ten mice and treating five of these mice with the aforementioned drug. The mice were observed for at least twelve days after injection.

In one series of experiments involving 120 mice, the dose of the organism was such that of the sixty untreated mice, fifty-six died and one was afflicted with arthritis. Of the sixty treated animals, only two died and four were afflicted with arthritis. The dosage of drug in this instance was 0.25 gm per kilogram of weight of the mouse. The amount of the gold preparation used appears to be rather large, but it was well tolerated by the mice.

In another set of experiments involving thirty mice, the amount of drug was reduced to 0.025 gm per kilogram of weight of the mouse. In this series thirteen of the fifteen untreated mice died, whereas of the fifteen treated mice, four died and six were afflicted with arthritis.

Four different strains of *Streptobacillus moniliformis* were used in these experiments. One of these strains was isolated from the blood of a patient who recently had rat-bite fever and the other three strains were isolated from rats. There was no noticeable difference in the therapeutic effectiveness of the gold compound on the infections experimentally produced by the use of these different strains.

The *in vitro* effect of the gold compound on the growth of the *Streptobacillus moniliformis* was found to be slight as compared with the *in vivo* activity of the compound. Twenty per cent. serum-veal infusion broth containing 0.125 per cent. of the gold compound caused a twenty-hour delay in the appearance of growth. When the broth contained 0.25 per cent., the final growth was decreased by one half. This drug caused some precipitation of the proteins of the medium, which may explain the effect on the growth of the microbe.

The organism was found to grow well in a medium consisting of soluble starch, proteose peptone and a number of salts. This medium contained much less protein than did the serum-veal broth and in this instance a concentration of the gold salt to 0.01 per cent. flocculated the medium and inhibited growth.

No therapeutic result was demonstrable with neoarsphenamine. In various experiments the drug was administered in amounts of 0.015 and of 0.03 gm per kilogram of weight of the mouse. It was administered by intravenous and by intra-abdominal injection, in some instances at the time of injection of the bacterial culture and in some instances six hours later.

Attempts to protect mice against experimental infection by the administration of sulfapyridine in the food were unsuccessful.[4, 5] Mice were placed on a diet of ground food mixed with 0.5 per cent. sulfapyridine for twelve, twenty-four and forty-eight hours before injection of the bacterial culture. In experi-

[1] Emmy Klieneberger, *Jour. Path. and Bact.*, 42: 587, 1936.
[2] Louis Dienes, *Jour. Infect. Dis.*, 65: 24, 1939.
[3] G. M. Findlay, R. D. Mackenzie, F. O. MacCallum and Emmy Klieneberger, *Lancet*, 2: 7, 1939.
[4] R. N. Bieter, W. P. Larson, E. M. Cranston and L. Levine, *Jour. Pharmacol. and Exper. Therap.*, 66: 3, 1939.
[5] J. Litchfield, White, H. and E. Marshall, *Jour. Pharmacol. and Exper. Therap.*, 66: 23, 1939.

ments involving fifty mice no favorable effect on mortality was observed in the treated group. In a small series of mice placed on a diet containing 1 per cent. sulfapyridine for forty-eight hours before injection, there appeared to be a prolongation of life by a few hours in the treated group over that of the control group. The final mortality, however, was not affected.

It appears that a single injection of gold sodium thiomalate (myochrysine) will protect mice against rapidly fatal doses of *Streptobacillus moniliformis*, whereas neoarsphenamine and sulfapyridine are ineffective against this organism.

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SCIENTIFIC APPARATUS AND LABORATORY METHODS

PATTERNS ON MAPS AND DRAWINGS BY THE CARBON TRANSFER PROCESS

THE preparation for photolithographic reproduction of large numbers of isorithmic maps at the Muskingum Climatic Research Center[1] has led to the development of a simple and inexpensive process for shading them in distinctive patterns of black and white. It was necessary that the method be suitable for rapid use by workers having no experience in mechanical drafting or related techniques, that it cover large and small areas equally well and that the result be suitable for photomechanical reproduction. Hand ruling and stippling proved too difficult and too slow and failed to produce uniform results. Commercial pattern transfer methods were also slow and too expensive for the large total areas to be covered.

The new method, called the carbon transfer process, used successfully for the past year, is reminiscent of the simple childhood amusement of putting a paper over a coin and reproducing the pattern by rubbing with a pencil. In the new method, however, the marking is done by carbon paper and the back of the copy is rubbed with any hard smooth burnisher.

Maps or drawings to be patterned should be on thin paper or the areas should be outlined on the back by tracing or by the use of carbon paper so that they can readily be followed. To pattern the desired areas, place a sheet of wire cloth or other master pattern on a desk blotter spread on a smooth hard table top. Lay a sheet of moderately soft typewriting carbon paper on the master pattern, *face up*, and on this the drawing to be patterned, *face down*. A few lead weights will help keep this drawing and carbon paper in position on the pattern. To transfer the pattern, tool or burnish the back of the drawing smoothly but firmly in the areas where this particular design is desired. The bowl of a teaspoon, rounded back of a comb, bone-type hairpin, toothbrush handle or other smooth firm tool can be used, depending on the shape and size of the areas to be covered and on the coarseness of the pattern. Spraying the completed pattern with a suitable artist's "fixatif" will prevent smudging.

A large variety of patterns are available. Embossed book covers in grain or line patterns will serve for temporary use. More permanent are window screening and other types of wire cloth which are produced in hundreds of sizes and weaves. The usual square weave of sizes from 2×2 to 80×80 to the inch in various materials and wire sizes were tried. The coarsest and finest meshes were difficult to tool evenly, but those of intermediate size gave very satisfactory patterns. Weaves of unequal mesh, such as the 6×24, 14×88, "twilled," "flat warp," "double crimp," "rolled top" and many other kinds are available from the large manufacturers of wire cloth and give a variety of special effects. Some of these screens give two or more designs, depending on the tool selected and the direction of stroke. For uniformity of result it is generally more satisfactory to use a combination that gives the same pattern regardless of direction of tooling.

Patterns of a different type can be obtained from the molded plates used for making designs on mimeograph stencils. For line patterns, printer's brass rule can be set to the desired weight of line and spacing and locked in a form. Individual lines or pairs of lines can be tooled across the area to be shaded more rapidly than they can be drawn with a ruling pen and straight edge. Square or diamond patterns can be obtained by a second tooling with the lines crossing the drawing at a different angle.

Periods, colons, dotted leaders or other symbols in printer's type can be set to provide almost any weight and spacing of dotted patterns. Stereotype castings can be made from the type and preserved for permanent use. This work can be done by almost any newspaper office, and extra stereotype mats can be obtained so that additional plates can be cast later at small expense if those in use become worn.

Several of the patterns obtained by the carbon transfer process are shown in Fig. 1. Patterns A, B and C are produced from stereotype plates cast from periods. Pattern U is from mimeograph plate No. 1648. All other patterns in Fig. 1 are produced from

[1] Operated jointly at New Philadelphia, Ohio, by the U. S. Soil Conservation Service, the Works Projects Administration, the Muskingum Watershed Conservancy District and the National Youth Administration, in cooperation with the U. S. Weather Bureau and the Ohio Agricultural Experiment Station. C. W. Thornthwaite, SCIENCE, 86: 2222, 100–101, July 30, 1937.

wire screen or cloth. Patterns R and S are both from the same screen, R being produced by vertical, and S by horizontal tooling.

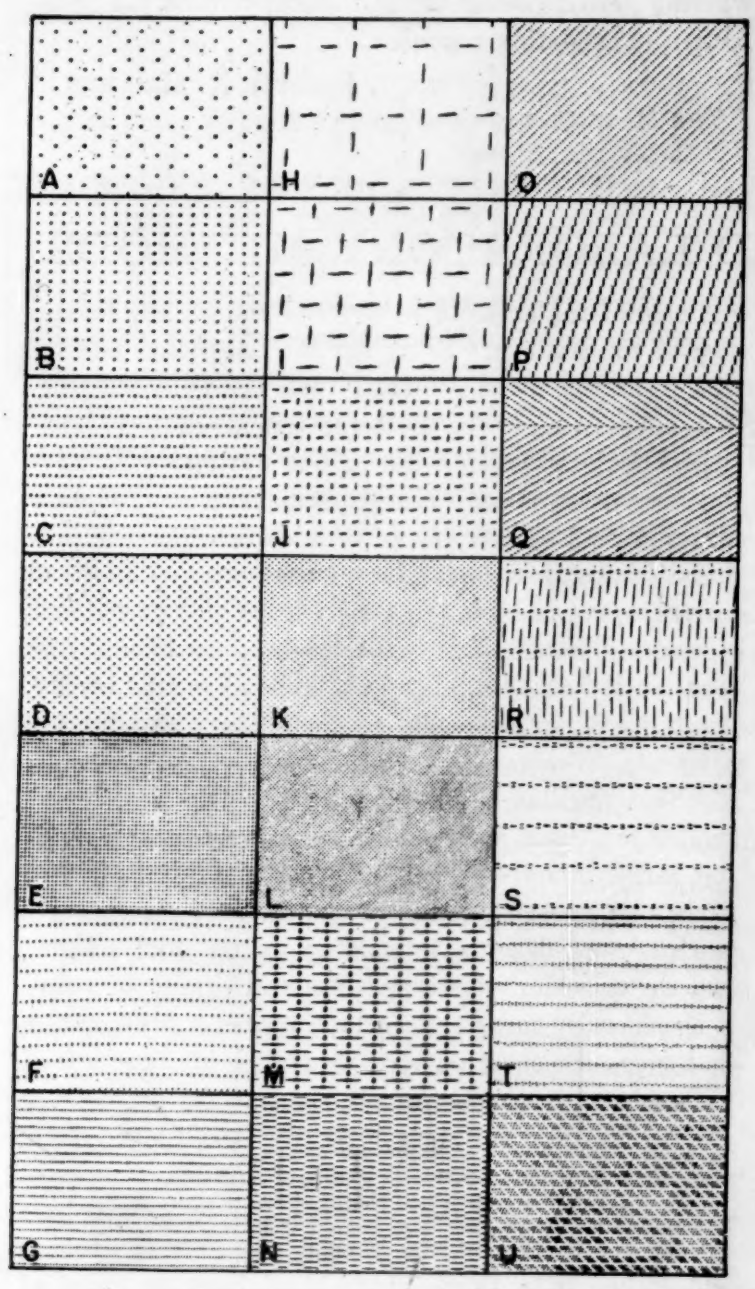

FIG. 1. Patterns from selected stereotype and mimeograph plates and wire cloth and screen. A–C: Stereotype plates cast from periods. A: Coarse, staggered; B: medium, not staggered; C: fine, staggered. D–T: Wire cloth and screen. D: 22×24 "flat warp;" E: 30×30; F: 8×38; G: 14×88; H: ½" opening, .063 wire, diamond; I: 4×4, .047 wire; J: 10×10, .025 wire; K. No. 40; L: 60×60, .008 wire; M: No. 617 "ton-cap"; N: No. 2475 "ton-cap;" O: 50×50 twilled, .011 wire; P: 14×40 twilled, .023 wire; Q: 60×40 twilled, herringbone; R: 3×14 (tooled vertically); S: 3×14 (tooled horizontally); T: 6×34 (tooled horizontally). U: Mimeograph plate No. 1648.

Five graded patterns (A through E) are used on the maps made at the Climatic Research Center (Fig. 2). These screens and stereotype plates have had almost daily use for more than a year and are still serviceable. Pattern D is from 22×24 mesh flat warp phosphor bronze wire cloth and pattern E from 30×30 mesh brass wire cloth. Finer meshes, such as were used for pattern L, tend to block up and will not stand much reduction.

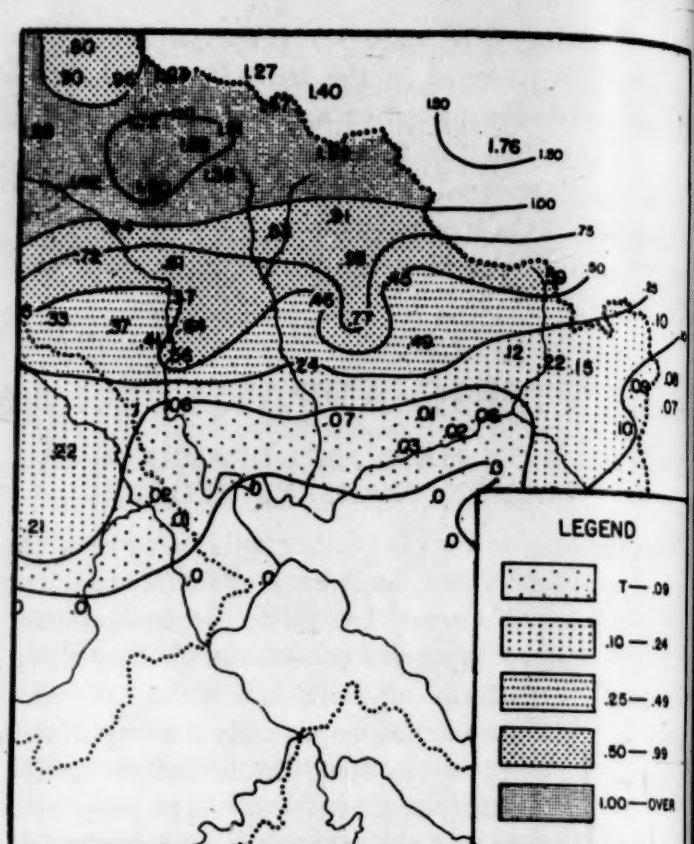

FIG. 2. Portion of precipitation map patterned by carbon transfer process at Muskingum Climatic Research Center (reduced about 2½ times from original).

The carbon transfer process can readily be adapted to special needs. It is useful not only for patterning on maps and graphs but for shading sketches such as those widely used in commercial illustration. Patterns made in this way can be reproduced by blue print, ozalid or photographic processes. Considering its simplicity, speed and relatively small cost, the carbon transfer method should be of use to workers in many branches of the physical and social sciences.

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